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(54) Salts of L-carnitine and alkanoyl L-carnitines and process for preparing same.

(57) Novel L-carnitine and alkanoyl L-carnitine salts and a process for their preparation are disclosed. The salts have general formula

$$(CH_3)_3N^+ CH_2C(X^-)_nOR\,HCH_2COOH$$

wherein

X^- ist an anion selected among acid aspartate, acid citrate, acid phosphate, acid fumarate, lactate, acid maleate, acid oxalate, acid sulphate and orotate;

R is hydrogen provided that X^- is other than orotate, or lower alkanoyl selected among acetyl, propionyl and butyryl; and

n is ½ if X^- is orotate, and 1 if X^- is one of the other anions.

Since they are not hygroscopic, these salts can be easily compounded and are favourably suitable for manufacturing solid administration forms. Their aqueous solutions are less acid than those of the corresponding chlorides: consequently, these salts are also suitable for manufacturing injectable administration forms.

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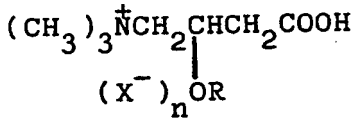
Salts of L-carnitine and alkanoyl L-carnitines and process for preparing same.

The present invention relates to non-hygroscopic salts of L-carnitine and alkanoyl L-carnitines having general formula



wherein X^- is an anion selected among acid aspartate, acid citrate, acid phosphate, acid fumarate, lactate, acid maleate, acid oxalate, acid sulphate and orotate;

R is hydrogen, provided that X^- is other than orotate, or lower alkanoyl selected among acetyl, propionyl and butyryl; and

n is 1/2 if X^- is orotate, and 1 if X^- is one of the other anions.

This invention also relates to a process for manufacturing such salts and to pharmaceutical compositions containing same.

It is well known that carnitine and its alkanoyl derivatives lend themselves to various therapeutical uses. It is also known that the salts of carnitine and of its alkanoyl derivatives possess the same therapeutical activities as those of the so-called "inner salts" and can, therefore, be used

in place thereof, provided that they are "pharmacologically acceptable" salts. So, pratically, the choice between the "inner salt" and a true carnitine or alkanoyl carnitine salt depends mostly on which compound is more easily or economically available and on pharmaceutical technology considerations rather than on therapeutical activity considerations.

It should be understood that, as far as the present invention is concerned, the utility of the foregoing salts does not consist in a therapeutical activity qualitatively or quantitatively different from the activities already known, but rather in their lack of hygroscopicity in comparison with the corresponding inner salts and chlorides, and in the higher pH of their solutions in comparison with the pH of the solutions of the corresponding chlorides. Because of their lack of hygroscopicity, these salts can be more easily handled and compounded, particularly with regard to the manufacture of solid administration forms, whilst the lower acidity of their solutions permits these salts to be used for preparing parenterally administrable forms, particularly via the intravenous route.

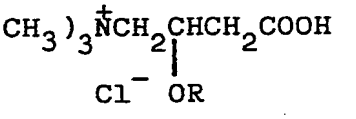
It is surprising and unexpected that the salts of L-carnitine and of alkanoyl L-carnitines according to this invention are not hygroscopic, because some corresponding salts of the racemic D,L form are known which are extremely hy-

groscopic and there is no theorical ground for believing that, if a certain salt of D,L-carnitine or alkanoyl D,L--carnitine is hygroscopic, also the same salt of the separated optycal isomers, particularly the salt of the L-isomer, should not be hygroscopic as well. Thus, e.g., while the known salts D,L-carnitine acid fumarate and D,L-carnitine acid oxalate (see Chem. Abst. 60, 12097, 1964) are hygroscopic, the novel salts of this invention, L-carnitine acid fumarate, and L-carnitine acid oxalate, are practically non hygroscopic.

It is also surprising and unexpected (since there are no theorical grounds for holding the contrary true) that when a certain salt of L-carnitine is hygroscopic, the corresponding salt of alkanoyl L-carnitine should not be hygroscopic as well. Finally, it is surprising and unexpected that when the L-carnitine salt with a certain polybasic acid is hygroscopic, the acid salt of L-carnitine or alkanoyl L--carnitine with the same polybasic acid is not hygroscopic at all. Thus, e.g., whereas the known salt L-carnitine phosphate is hygroscopic (see Medical Journal of Osaka University, 21, No. 1, December 1970, pages 7-12), the novel salts according to this invention L-carnitine acid phosphate and acetyl L-carnitine acid phosphate are not hygroscopic.

The process for producing the salts according to this invention comprises:

(a) converting in a per se known manner a chloride of general formula



wherein R has the previously defined meaning, to the corresponding inner salt;

(b) reacting an aqueous or alcoholic solution of said inner salt at a temperature between room temperature and about 50°C, with an equimolar amount of an acid selected among aspartic, citric, phosphoric, fumaric, lactic, maleic, oxalic and sulphuric acid or with a semi-molar amount of orotic acid, thus obtaining the desired salt; and

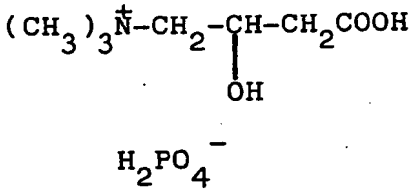
(c) isolating the desired salt by concentration of the alcoholic solution or concentration or lyophilization of the aqueous solution and optionally subsequent crystallization.

As stated before, the conversion of the chloride in step (a) to the corresponding inner salt can be carried out via known procedures. For instance, a typical procedure is described by E. Strack in "Darstellung von O-acyl-carnitinen", Hoppe-Seyler's Z. Physiol. Chem., 351, 95-98, January 1970. Alternatively, the conversion can be carried out as disclosed in the Italian patent application 24432A/82 jointly filed on November 25, 1982 by SIGMA-TAU Industrie Farmaceutiche Riunite S.p.A. and DE NORA S.A.

The following non-limiting examples illustrate the preparation of some non hygroscopic salts according to the present invention.

EXAMPLE 1

Preparation of L-carnitine acid phosphate (ST 521)



L-carnitine inner salt (200 g; 1.2 moles) was dissolved in the least necessary amount of water. To the solution 86% H_3PO_4 (61 ml; 1.2 moles)was added; the solution was then concentrated under vacuum and the residue was crystallized from isopropanol. The title compound was obtained as a non hygroscopic solid.

$[\alpha]_D^{25} = -20$ (C = 1 H_2O)

pH = 3

M.P. 145-150°C (softening at 80°C)

NMR D_2O δ 4.5 (covered, CH); 3.4 (2H, d, $\equiv\overset{+}{N}-CH_2$);

OH

3.2 (9H, s, $(CH_3)_3\overset{+}{N}$); 2.5 (2H, d, $-CH_2COOH-$).

EXAMPLE 2

Preparation of acetyl L-carnitine acid L-aspartate (ST 450)

Acetyl L-carnitine inner salt (7.2 g; 0.035 moles) was dissolved in water (50 cc). To the solution L-aspartic acid (4.7 g; 0.035 moles) was added and the solution was diluted with water to 800 cc. A complete dissolution of the mixture was obtained. The solution was lyophilized. A non-hygroscopic residue was obtained (11 g) consisting of the acetyl L-carnitine salt with aspartic acid.

$[\alpha]_D^{25} = -17.2$ (C = 1, H_2O)

pH = 3.5 5% H_2O solution

NMR D_2O δ 5.5 (1H, m, $-\underset{\underset{O}{|}}{CH}-$); 4.0-3.5 (3H, $-\underset{\underset{NH_2}{|}}{CH}-$; $\overset{+}{N}-CH_2-$);

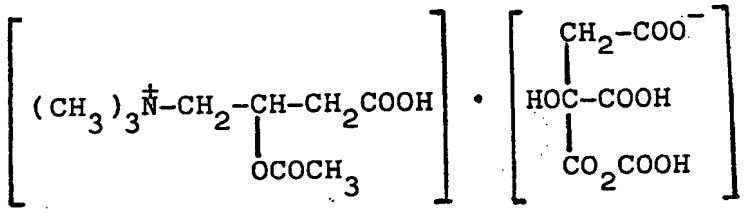
3.2 (9H, s, $CH_3-\overset{CH_3}{\underset{CH_3}{\overset{|}{\overset{+}{N}}}}$); 3.9-2.5 (4H, m, $-\underset{\underset{NH_2}{|}}{CH}CH_2$;

$-CH_2COOH$).

crystallized from isoprOH/Et_2O M.P. 190-195°C.

EXAMPLE 3

Preparation of acetyl L-carnitine acid citrate (ST 455)



A solution of acetyl L-carnitine chloride (2.4 g; 0.01 moles) in methanol was kept under stirring with Amberlite 26 activated in OH^- form (14 g) for 48 hours. The disappearance of the chloride ions from the methanol solution was checked. Monohydrated citric acid (2.1 g; 0.01 moles) was then added. The solution was concentrated to dryness under vacuum. 4.5 grams of a non-hygroscopic product consisting of the title compound were obtained.

NMR D_2O δ 5.6 (1H, m, $-\underline{CH}-$); 3.8 (2H, m, $\geqslant\overset{+}{N}-\underline{CH_2}-$);

3.2 (9H, s, CH_3, CH_3, CH_3 $\geqslant\overset{+}{N}$);

2.9-2.7 (6H, s and d, $OH\underline{C}$; $-\underline{CH_2}COOH$);

2.2 (3H, s, $-COCH_3$)

$[\alpha]_D^{25} = -16$ C = 1 H_2O

pH = 2.9 5% H_2O

EXAMPLE 4

Preparation of acetyl L-carnitine acid maleate (ST 456)

Acetyl L-carnitine inner salt (10.1 g; 0.05 moles) was dissolved in water. To the solution, maleic acid (5.8 g; 0.05 moles) was added. The solution was lyophilized. A hygroscopic solid was obtained which was repeatedly washed with anhydrous acetone. The residue was oven-dried under vacuum. 8 grams of the title compound as a non hygroscopic solid were obtained.

$[\alpha]_D^{25} = -22$ (C = 1 H_2O)

M.P. = 120° - 123°C

pH = 2.7 5% H_2O solution

NMR D_2O δ 6.3 (2H, s, -CH=CH-); 5.6 (1H, m, -CH(OCO-)-);

3.8 (2H, m, $\geq\overset{+}{N}-CH_2-$); 3.3 (9H, s, $(CH_3)_3\overset{+}{N}$);

2.9 (2H, d, $-\underline{CH_2}-COOH$); 2.1 (3H, s, $-COCH_3$)

H.P.L.C.

column	licrosorb NH_2
detector	U.V. 205 nm
mobile phase	$(NH_4)_2HPO_4$ 0.01M - CH_3CN (40-60) pH 7.8 with H_3PO_4 conc.
pressure	45 atm.
flow rate	2 ml/min

chart speed	0.5 cm/min
R_F	acetyl carnitine 1.0 cm
	maleic acid 1.5 cm

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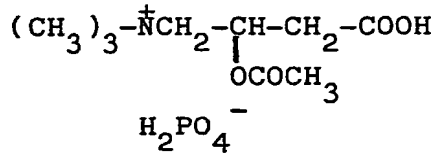
EXAMPLE 5

Preparation of acetyl L-carnitine acid phosphate (ST 451)

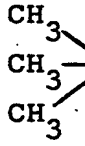


Acetyl L-carnitine inner salt (7.2 g; 0.035 moles) was dissolved in 50 cc of H_2O. To the resulting aqueous solution 85% H_3PO_4 (2.1 ml; 0.035 moles) was added. The aqueous solution was lyophilized and the residue was washed with anhydrous acetone. The product was dried under vacuum yielding 7.8 g of the non-hygroscopic title compound.

$[\alpha]_D^{25}$ = -17.7 (C = 1, H_2O)

M.P. = 155-157°C

pH = 2.75 5% H_2O solution

NMR D_2O δ 5.6 (1H, m, ); 3.8 (2H, m,); 3.2 (9H, s, ); 2.8 (2H, d, $C\underline{H}_2COOH$); 2.2 (3H, s, $-COCH_3$)

$C_9H_{20}NO_8P$

Calculated	Found	
C 35.87	34.95	
H 6.69	6.58	Cl <0.2%
N 4.64	4.50	
P 10.28	10.5	

EXAMPLE 6

Preparation of acetyl L-carnitine acid fumarate (ST 468)

Acetyl L-carnitine inner salt (4.95 g; 0.025 moles) was dissolved in 100 cc of H_2O. To the resulting solution fumaric acid (2.82 g; 0.025 moles) was added and the solution was lyophilized. 3.5 grams of a solid consisting of non-hygroscopic acetyl L-carnitine acid fumarate were obtained.

$[\alpha]_D^{25} = -22.7$ (C = 1 H_2O)

pH = 3.3 0.5% H_2O solution

NMR D_2O δ 6.6 (2H, s, $-\underline{CH}=\underline{CH}-$); 5.5 (1H, m, $-\underset{\underset{O}{|}}{CH}-$);

3.8 (2H, m, $\geqslant\overset{+}{N}-CH_2-$); 3.2 (9H, s, $(CH_3)_3\overset{+}{N}-$);

2.6 (2H, d, $-CH_2COO$); 2.1 (3H, s, $-COCH_3$).

M.P. 159-161°C.

EXAMPLE 7

Preparation of propionyl L-carnitine acid fumarate (ST 522)

Propionyl L-carnitine chloride (2.67 g; 0.01 moles) was dissolved in 10 cc of H_2O and the solution eluted through a column of IRA 402 Amberlite resin activated in HCO_3^- form (20 cc). 80 cc of an aqueous solution containing propionyl L-carnitine inner salt were collected. To this solution, fumaric acid (1.16 g; 0.01 moles) dissolved in 20 cc of H_2O was added. The solution was heated up to 50°C and kept at this temperature for 1 hour. The solution was then lyophilized. The lyophilized product was crystallized from isopropanol. The title compound was obtained as non hygroscopic solid.

$[\alpha]_D^{25}$ = -20.9 (C = 1 H_2O), M.P. 122-125°C.

NMR D_2O δ 6.6 (2H, s, -CH=CH-); 5.6 (1H, m, $-\underset{\underset{O-}{|}}{CH}-$);

3.8 (2H, m, $-\overset{+}{N}-CH_2-$); 3.3 (9H, s, $(CH_3)_3\overset{+}{N}$);

2.8-2.3 (4H, m, $-\underline{CH_2}COOH$; $-\underline{CH_2}CH_3$);

1.2 (3H, t, $CH_2\underline{CH_3}$)

$C_{14}H_{23}O_8N$

Calculated	Found
C % 50.44	49.80
H % 6.95	7.32
N % 4.20	4.05

EXAMPLES 8 - 10

By following the procedures of the previous examples, the following salts were prepared, whose melting point and optical rotatory power are indicated.

Example 8 : L-carnitine acid fumarate

M.P. 137-139°C (in ethanol)

$[\alpha]_D^{20}$ = -16 (C = 2.5 H_2O)

Example 9 : L-carnitine acid oxalate

M.P. 115-118°C (in ethanol)

$[\alpha]_D^{20}$ = -20 (C = 2.5 H_2O)

Example 10: L-carnitine acid sulphate

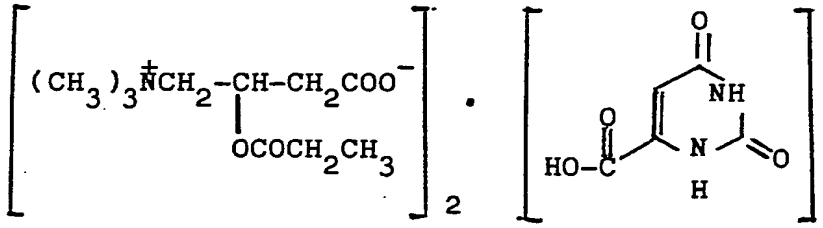
M.P. 109-113°C (in ethanol)

$[\alpha]_D^{20}$ = -18.5 (C = 2.5 H_2O)

It was found that all the compounds of the Examples 8-10 were non-hygroscopic.

EXAMPLE 11

Preparation of propionyl L-carnitine orotate (ST 552)



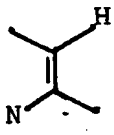
Propionyl L-carnitine inner salt (42.4 g; 0.2 moles) and orotic acid (17.4 g; 0.1 moles) were dissolved in methanol (200 cc). The solution was kept under stirring at room temperature for about 1 hour and then concentrated to dryness under vacuum. A white solid consisting of the salt of propionyl L-carnitine with orotic acid (2:1 ratio) was obtained.

HPLC VARIAN

Column:	μ Bondapak NH_2	
eluent:	KH_2PO_4 0.05M	35
	CH_3CN	65
pressure:	60 atm.	
flow rate:	1.5 ml/min	
U.V. detector:	205 λ	
integrator:	4270 Varian	
chart speed	0.5 cm/min.	
orotic acid:	Rf 2.70 cm	
Propionyl L-carnitine:	Rf 4.95 cm	

The ratio between orotic acid and propionyl L-carnitine (calculated from the ratio of the surface areas with reference to a standard) proved to be 32%:78%, whereas the theorical value calculated for the salt consisting of 2 moles of propionyl carnitine and 1 mole of orotic acid is 29%:71%. The salt proved to be hydrosoluble forming a 5% solution. This solution was stable for about 24 hours.

$[\alpha]_D^{25} = -23$ (H_2O)

NMR D_2O δ 6.3 (1H, s, ); 5.8 (2H, m, $(-\underset{\underset{O}{|}}{CH}-)_2$);

3.9 (4H, m, $(\overset{+}{N}-CH_2)_2$); 3.3 (18H, s, $((CH_3)_3\overset{+}{N})_2$);

2.9 (4H, d, $(CH_2CO)_2$); 2.6 (4H, q, $(OCOCH_2-)_2$);

1.3 (6H, t, $(-CH_3)_2$).

EXAMPLES 12-13

By following the procedures of Example 11, the following salts were prepared. Their optical rotatory power is hereinbelow indicated:

Example 12: acetyl L-carnitine orotate

$[\alpha]_D^{20} = -25$

Example 13: butyryl L-carnitine orotate

$[\alpha]_D^{20} = -15$

The present invention further comprises the pharmaceutical compositions containing at least one of the previously mentioned non-hygroscopic salts as active principle, and a pharmacologically acceptable solid or liquid excipient. In particular, the solid compositions which are suitable for preparing orally administrable dosage forms are preferred. For instance, a composition suitable for manufacturing tablets is the following:

L-carnitine non-hygroscopic salt according to the invention	mg 500
Starch	mg 20
Talc	mg 10
Ca-stearate	mg 1
	mg 531

The following is a composition suitable for manufacturing capsules:

L-carnitine non-hygroscopic salt according to the invention	mg 380
Lactose	mg 50
Starch	mg 20
Talc	mg 5
Ca-stearate	mg 2
	mg 457

CLAIMS

1. L-carnitine and alkanoyl L-carnitine non hygroscopic salts of general formula:

$$(CH_3)_3\overset{+}{N}CH_2\underset{(X^-)_n}{\overset{|}{C}}HCH_2COOH$$
$$OR$$

wherein X^- is an anion selected among acid aspartate, acid citrate, acid phosphate, acid fumarate, lactate, acid maleate, acid oxalate, acid sulphate and orotate;

R is hydrogen provided that X^- is other than orotate, or lower alkanoyl selected among acetyl, propionyl and butyryl; and

n is 1/2 if X^- is orotate, and 1 if X^- is one of the other anions.

2. A process for producing a salt of claim 1, which comprises:

(a) converting in a per se known manner a chloride of general formula

$$(CH_3)_3\overset{+}{N}CH_2\underset{Cl^-}{\overset{|}{C}}HCH_2COOH$$
$$OR$$

wherein R has the previously defined meaning, to the corresponding inner salt;

(b) reacting an aqueous or alcoholic solution of said inner salt at a temperature between room temperature and about 50°C, with an equimolar amount of an acid selected among aspartic, citric, phosphoric, fumaric, lactic, maleic, oxalic and sulphuric acid or with a semi-molar amount of orotic acid, thus obtaining the desired salt; and

(c) isolating the desired salt by concentration of the alcoholic solution or concentration or lyophilization of the aqueous solution and optionally subsequent crystallization.

3. A pharmaceutical composition comprising a salt of claim 1 as active principle and a pharmacologically acceptable solid or liquid excipient therefor.

4. The composition of claim 3 in solid form.

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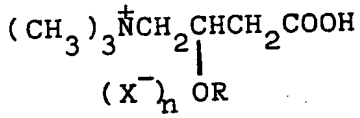
Single claim for Austria (under the provision of art. 167(2)(a) EPC).

CLAIM

A process for producing L-carnitine and alkanoyl L-carnitine non hygroscopic salts of general formula:

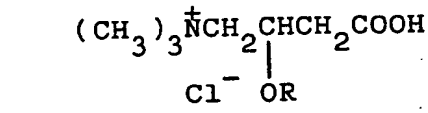


wherein X^- is an anion selected among acid aspartate, acid citrate, acid phosphate, acid fumarate, lactate, acid maleate, acid oxalate, acid sulphate and orotate;

R is hydrogen provided that X^- is other than orotate, or lower alkanoyl selected among acetyl, propionyl and butyryl; and

n is 1/2 if X^- is orotate, and 1 if X^- is one of the other anions, which comprises:

(a) converting in a per se known manner a chloride of general formula



wherein R has the previously defined meaning, to the corresponding inner salt;

(b) reacting an aqueous or alcoholic solution of said inner salt at a temperature between room temperature and

about 50°C, with an equimolar amount of an acid selected among aspartic, citric, phosphoric, fumaric, lactic, maleic, oxalic and sulphuric acid or with a semi-molar amount of orotic acid, thus obtaining the desired salt; and

(c) isolating the desired salt by concentration of the alcoholic solution or concentration or lyophilization of the aqueous solution and optionally subsequent crystallization.

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Application number

European Patent Office

EUROPEAN SEARCH REPORT

EP 84830329.3

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	CHEMICAL ABSTRACTS, vol. 60, May 11 - June 22, 1964 Columbus, Ohio, USA YOSHIKAZU OKA et al., "Carnitine derivatives" columns 12 097 und 12 098 g,h & Takeda Kenkyusho Nempo 22, pages 13-18 (1963) --	1	C 07 C 101/30 A 61 K 31/195
A	GB - A - 1 153 640 (SOCIETE D'ETUDES DE PRODUITS CHIMIQUES) * Totality * ----	1-4	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 C 101/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	29-03-1985	HEIN

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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